REMARKS

Upon entry of this amendment, claims 2, 3, 5, 7, 8, 39-43, 45-57 and 59-72 are pending in the application. New claims 69-72 have been added. Support for new claims 69 and 71 can be found throughout the specification, *e.g.*, at least at page 7, lines 14-16; page 10, lines 5-6; and at page 44, lines 1-2 of the specification. Support for new claims 70 and 72 can be found at least at page 9, lines 10-13. No new matter has been added.

Rejections under 35 U.S.C. § 112, first paragraph, written description

Claims 2, 3, 5, 7, 8, 39-43, 45-57 and 59-68 are rejected under 35 U.S.C. § 112, first paragraph for allegedly lacking written description. According to the Examiner, the teachings of the specification do not address the method of modulating activation of an NFκB signaling pathway in a cell already having TRADE activity. According to the Examiner, the agent that stimulates the expression of the TRADE transcription does not require the cell to possess TRADE activity, as a cell that does not have TRADE activity can be transfected with an expression cassette. *See*, Advisory Action at Continuation Sheet. Applicants respectfully disagree and maintain that the specification provides adequate written description for the claimed invention.

An objective standard for determining compliance with the written description requirement under 35 U.S.C. § 112, first paragraph, is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, the Applicant was in possession of the invention as now claimed. *Vas-Cath, Inc. v. Mahurkar,* 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991) and *In re Gosteli,* 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). That is, the disclosure must show that the inventor(s) had ***invented each feature that is included as a claim limitation***. *New Railhead Mfg., L.L.C. vl. Vermeer Mfg. Co.,* 298 F.3d 1290, 63 USPQ2d 1843 (Fed. Cir. 2002) (emphasis added).

The Examiner is reminded that there is a strong presumption that an adequate written description of the claimed invention is present when the application is filed. *See*, *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976).

First, the specification describes that "TRADE activity" includes the ability to modulate (*e.g.*, increase or decrease a particular parameter being described) cell proliferation (*e.g.*, by enhancing proliferation or apoptosis) and/or the ability to modulate an NFκB signaling pathway,

and/or the ability to modulate a JNK signaling pathway in a cell. *See*, Specification at page 11, lines 1-13. Moreover, the specification discloses cells that have TRADE activity, such as the various tissues and organs that express human TRADE. *See*, Specification at page 8, line 29 to page 9, line 5. Finally, the specification describes various methods of modulating TRADE activity by contacting a cell with an agent that modulates TRADE expression and/or activity such that TRADE expression and/or activity in the cell is modulated. *See*, Specification at page 19, line 18 to page 25, line 2. Based on the specification and the original filed claims, it would be clear to one of skill in the art that only cells with TRADE activity will respond to the administration of an extracellular portion of the TRADE polypeptide.

Second, the specification provides adequate description of a soluble form of a TRADE polypeptide comprising a TRADE polypeptide extracellular domain. *See*, Specification at page 3, lines 1-2. Specifically, the specification describes that soluble forms of TRADE polypeptide can be used as TRADE ligand antagonists. *See*, Specification at page 49, lines 14-18.

Third, original claims 6, 16, 18, 20, and 25 of the application recite as follows (emphasis added):

> 6. The method of claim 2, wherein the agent is a **soluble** form of a TRADE polypeptide comprising a TRADE polypeptide **extracellular domain**.
>
> 16. A method of modulating the proliferation of a cell comprising contacting the cell with an agent that **modulates the activity** of a TRADE family member polypeptide, wherein the cell is selected from the group consisting of: an epithelial cell, a ductal epithelial cell, a carcinoma cell, and an adenocarcinoma cell such that the proliferation of the cell is modulated.
>
> 18. The method of claim 15 or 16, wherein the agent is a **soluble** form of a TRADE family polypeptide comprising a TRADE **extracellular domain**.
>
> 20. The method of claim 15 or 16, wherein the agent consists essentially of a TRADE family **extracellular domain**.
>
> 25. The method of claim 16, wherein the activity is selected from the group of activities consisting of: activation of a **JNK signaling pathway**, activation of an **NFkB signaling pathway**, and activation of **apoptosis**.

The law is clear that, if a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing, even if not

every nuance of the claims is explicitly described in the specification, then the adequate written description requirement is met.[1]

With specification and original claims in hand, one skilled in the art would understand that the claimed methods for modulating TRADE activity in a cell with an agent that modulates TRADE expression and/or activity, specifically require that the cell actually possess TRADE activity that can be modulated. As such, the instant specification provides adequate support for a method for modulating activation of an NFkB signaling pathway in a cell by contacting a cell having TRADE activity with a TRADE polypeptide, as required by the pending claims.

For these reasons, Applicants contend that one ordinarily skilled in the art of cell proliferation and apoptosis would believe that Applicants were in possession of the claimed invention. This rejection should be withdrawn.

Rejections under 35 U.S.C. § 112, first paragraph, enablement

Claims 2, 3, 5, 7, 8, 39-43, 45-57 and 59-68 are rejected under 35 U.S.C. § 112, first paragraph for allegedly failing to comply with the enablement requirement. According to the Examiner, the specification fails to describe a soluble form of a TRADE polypeptide that is encoded by a polynucleotide at least 98% homologous to a polynucleotide encoding amino acids 1-168 of SEQ ID NO: 2, which functions as an antagonist of a TRADE ligand, thereby modulating NFκB activation in a cell. *See*, Advisory Action at Continuation Sheet. This rejection is respectfully traversed as it is applied to the pending claims.

Independent claims 2 and 53, from which the remaining claims subject to the rejection depend, recite a method for modulating activation of an NFκB signaling pathway by contacting a cell having TRADE activity with a soluble form of a TRADE polypeptide comprising the extracellular domain of a TRADEα polypeptide.

First, the specification describes isolated nucleic acid molecules encoding TRADE or portions thereof. *See*, Specification at page 27, line 24 to page 43, line 16. Specifically, the specification describes an isolated nucleic acid molecule which is at least about 98% homologous to the nucleotide sequence encoding a TRADE family polypeptide or a portion thereof, *e.g.*, an extracellular domain. *See*, Specification at page 31, lines 18-24.

[1] *In re Alton* 76 F.3d 1168, 37 USPQ2d 1578 (Fed. Cir. 1996).

Isolated TRADE proteins, fragments thereof and anti-TRADE antibodies are described at least at page 43, line 19 to page 66, line 28 of the specification. Specifically, a TRADE extracellular domain comprising amino acid residues corresponding to residues 1-168 of SEQ ID NO: 2 is described at least at page 7, lines 12-16. The specification describes that soluble TRADE peptides comprising the extracellular portion of the TRADE protein act as antagonists to TRADE ligand. *See*, Specification at page 130, line 16 to page 131, line 6 and at Example 6. The antagonism of TRADE ligand induces the modulation of activity of the intracellular portion of the TRADE proteins expressed in a cell to which the soluble TRADE extracellular protein is administered.

Moreover, an exemplary protocol for molecular cloning and genetic mapping of TRADE is described in Example 1, while Figure 1 depicts the amino acid sequence comparison between the two human TRADE proteins of the invention (α and β). Recombinant expression vectors and host cells for expressing TRADE proteins or protein fragments in prokaryotic or eukaryotic cells is described at page 67, line 1 to page 76, line 15 of the specification.

Second, the specification discloses various different TRADEα polypeptides, *e.g.*, Flag-TRADEα, Flag-TRADE 1-368, Flag-TRADE 1-328, Flag-TRADE 1-218 and Flag-TRADE 1-196, which modulate the activity of NFκB. *See*, Specification at page 133, lines 8-24 and at Figure 9 and 14A. Example 4 of the specification describes that increasing the expression of TRADE leads to modulation of NFκB and JNK activity. *See*, Specification at page 126, lines 18-26 and at page 127, line 21 to page 128, line 5. TRADE activity is described in detail at page 11, lines 1-14, and the NFκB signaling pathway is described at page 11, line 23 to page 12, line 2. Accordingly, the specification provides various examples of TRADEα polypeptides comprising a TRADEα extracellular domain that have the ability to modulate NFκB signaling.

Third, Examples 2 and 3 demonstrate TRADEα and TRADEβ expression in various tissues and organs with the highest levels in adult prostate, lung, ovary, and fetal lung and liver. Immunohistochemistry demonstrated that TRADEα and TRADEβ are expressed in the prostate, parotid gland and testis to ductal epithelial tissues, and that TRADE expression can be detected in adenocarcinomas.

Finally, Applicants note that the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. *See*, MPEP § 2164.08(b). The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally

required in the art. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984) (prophetic examples do not make the disclosure nonenabling). Furthermore, as described above, the examples detailed in the specification provide evidence for clear enablement of the claimed methods.

Therefore, Applicants submit that, contrary to the Examiner's contention, as of the filing date of the instant invention, the pending claims are fully enabled by the as-filed specification. Thus, this rejection should be withdrawn.

On the basis of the foregoing amendments and remarks, Applicants submit the pending claims are in condition for allowance. Such action is respectfully requested. A Petition for a Five Month Extension of Time is filed herewith, along with the appropriate fee. With this extension, these papers are due on or before March 11, 2009.

The Commissioner is authorized to charge any fees that may be due, or credit any overpayment of same, to Deposit Account No. 50-0311, Reference No. 22058-569001US.

Respectfully submitted,

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